Dopamine Gene Variants Predict Response to Aripiprazole in Individuals

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Technology description

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Since medications that can control, regulate, or change the brain dopamine system might be beneficial in treating Alcohol Use Disorder (AUD), MUSC investigators studied the anti-drinking effect of a marketed brain dopamine acting medication, aripiprazole, in individuals with AUD who were genotyped for variants in several brain-functional dopamine system genes including: the dopamine transporter gene (DAT1) variable nucleotide tandem repeat (VNTR 9R vs. 10R), the dopamine 4 receptor (DRD4) long (>7) vs, short (<7) VNTR’ s), catechol-o-methyl transferase (COMT) (val158met SNP), and a dopamine D2 receptor SNP (rs 1076560). They found that the DAT1 genotype is most critical for the amount of drinks in non-treatment seeking individuals. In addition, an additive effect was found with additional gain of function dopamine alleles that demonstrate an added effect on the ability of aripiprazole to reduce drinking behavior (data not shown). As a whole, these brain dopamine system alleles can help inform AUD trials, guide development of new pharmacotherapies and be used as a diagnostic test to identify specific individuals that are most likely to benefit from dopaminergic based medications.

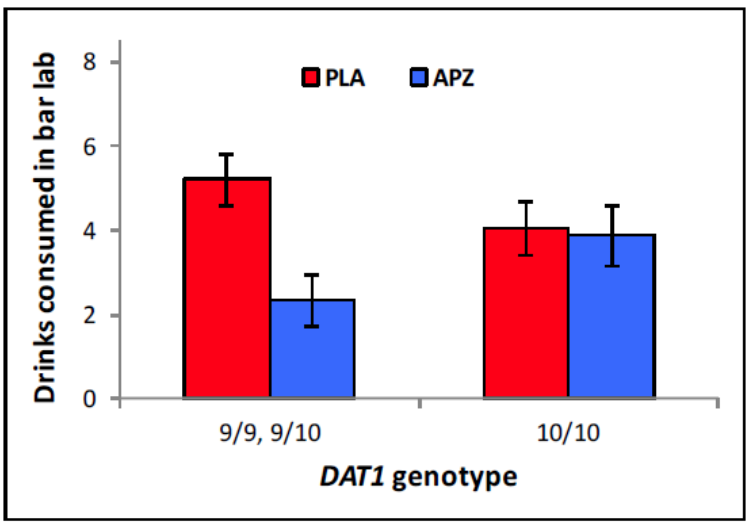

Figure 1. Effects of medication and *DAT1* genotype on bar-lab drinking. There was a significant main effect of medication ($F(1, 76) = 5.27$, $p = .024$) and an interaction between medication and genotype ($F(1, 76) = 4.07$, $p = .047$). APZ reduced drinking among 9R carriers, but was not significantly different from placebo for 10R homozygotes.

Overview

According to the National Institute for Alcohol Abuse and Alcoholism (NIAAA), 6.2 percent of adults in the US had an alcohol use disorder (AUD) in 2015. Medications available to treat AUD are not universally efficacious and in group studies have small to moderate effect sizes. Dopamine is one

neurotransmitter thought to play a crucial role in the development and maintenance of AUD. Within the dopamine system there are a number of putative functional genetic variants influencing its production in the brain including receptor binding, synaptic abundance, breakdown, and that potentially might predict medication response. Clinical trials of dopaminergic medications, including the dopamine partial agonist aripiprazole (APZ), have been mixed, and positive effects highly variable. This suggests that genetic diversity may influence the effectiveness of dopaminergic medications for AUD and other conditions.

Key Words:AUD, alcohol use disorder, alcoholism, pharmacotherapy, aripiprazole, D2, DRD4. COMT, DAT1, SLC6A3, dopamine system, dopaminergic partial agonist, alcohol, addiction

Publication:

Schacht JP et al., (2018). Dopaminergic Genetic Variation Influences Aripiprazole Effects on Alcohol Self-Administration and the Neural Response to Alcohol Cues in a Randomized Trial . Neuropsychopharmacology. doi: 10.1111/adb.12676.

Background Publication:

Anton RF et al., (2008). A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. J Clin Psychopharmacol, 28(1):5-12.

Application area

Companion diagnostic, informing AUD treatment and AUD clinical trials, drug discovery.
Determine groups more likely to respond to dopaminergic compounds for multiple applications, including AUDs Key Words: AUD, alcohol use disorder, alcoholism, pharmacotherapy, aripiprazole, D2, DRD4. COMT, DAT1, SLC6A3, dopamine system, dopaminergic partial agonist, alcohol, addiction

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